The Reaction of *N*-Acetylisatin with Amines

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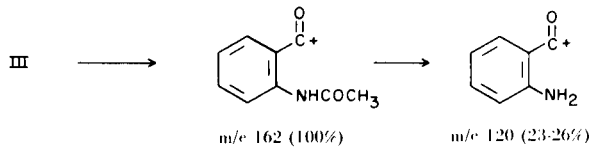
While it is well known (1) that isatin and primary amines react to give compounds of the type I, the similar reaction of *N*-acetylisatin has received relatively little attention. Parisi (2) has reported that *N*-acetylisatin and anilines gave II (R = C_6H_5) but Meyer (3) observed that *N*-acetylisatin with ammonia gave III (R = H).

In this work we wish to report that the reaction of *N*-acetylisatin with equimolar quantities of several primary amines did not give rise to compounds of the type II but rather to compounds of structure III. The compounds of the type III are included in Table I. The infrared, nuclear magnetic resonance, and mass spectral data are all consistent with structure III. The mass spectra of III (R = *n*-butyl and cyclopentyl) show very weak molecular ions (2%) and the following highly favored fragmentation process:

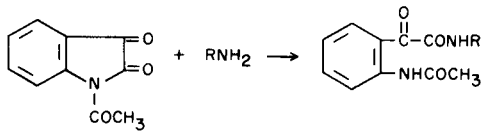


m/e 162 (100%) m/e 120 (23-26%)

The nmr shows two exchangeable protons, the one at 11.3 δ being assigned to the acetylamide proton on the basis of the nmr of *o*-acetylacetanilide (4). The other NH which exchanges at a slower rate, is found in the aromatic region.

Meyer (3) has observed that *N*-acetylisatin and an excess of ammonia led to a quinazoline derivative. Reaction of *N*-acetylisatin with a ten-fold excess of a primary amine gave a series of compounds of the type IV (R = R′). Compound IV (R = R′) was also formed by reaction of III with an excess of the same amine used to prepare III. Reaction of III with a different amine or with phenylhydrazine gave IV (R ≠ R′). Hydrolysis of IV with 5% hydrochloric acid gave rise to III. Compounds of the type IV are included in Table II. The infrared, nuclear magnetic resonance and mass spectral data are consistent with structure IV. The mass spectra of IV show very weak molecular ions (3-6%), as did III, and the following highly favored fragmentation process:

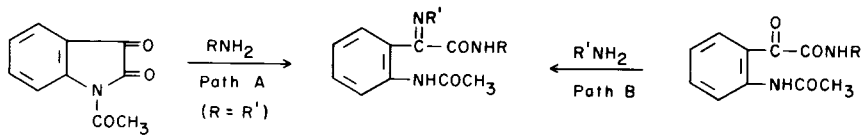
TABLE I



R	M.p. (a)	Yield %	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR(KBr), cm^{-1}		
H	212-214 (b)	43	$C_{10}H_{10}N_2O_3$							3290	1690	1655
Ethyl	128-130	50	$C_{12}H_{14}N_2O_3$	61.54	6.02	11.95	61.54	6.01	11.94	3230	1690	1665
n-butyl	115-116	25	$C_{14}H_{18}N_2O_3$	64.10	6.92	10.68	64.42	6.94	10.55	3290	1695	1665
Cyclopentyl	150-151	22	$C_{15}H_{18}N_2O_3$	65.67	6.61	10.21	65.71	6.52	10.13	3245	1695	1665
Phenyl	177-178 (c)	59	$C_{16}H_{14}N_2O_3$	68.07	4.99	9.92	68.41	5.10	9.98	3240	1695	1675
Ethyl (d)	185-186	41	$C_{13}H_{16}N_2O_3$	62.89	6.50	11.28	62.85	6.52	11.29			

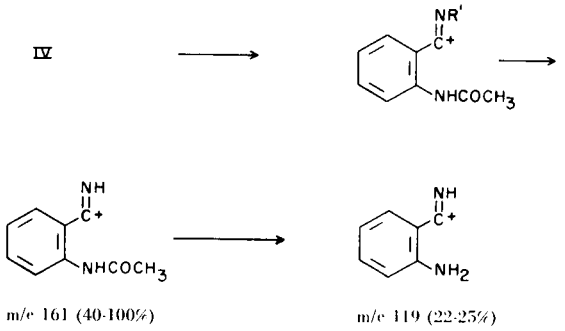
(a) Recrystallized from cyclohexane unless otherwise noted. (b) Reported (3) m.p. 215-216°; recrystallized from ethyl acetate. (c) Recrystallized from ethanol. (d) *N*-acetyl-5-methylisatin used in place of *N*-acetylisatin.

TABLE II



R	R'	Path	M.p. (a)	Yield	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR(KBr), cm^{-1}			
Et	Et	A	178-179	49	$C_{14}H_{19}N_3O_2$	64.34	7.33	16.08	64.08	7.23	16.12	3240	3050	1680	1616
Et	Et	B		36											
n-Bu	*n*-Bu	A	85-86 (b)	68	$C_{18}H_{27}N_3O_2$	68.10	8.57	13.24	67.71	8.71	13.04	3190	3030	1665	1625
n-Bu	*n*-Bu	B		100											
C_5H_9	C_5H_9	A	185-186	59	$C_{20}H_{27}N_3O_2$	70.39	7.97	12.31	70.61	8.01	12.18	3225	3030	1670	1615
C_5H_9	C_5H_9	B		90											
n-Bu	Et	B	137-139 (b)	91	$C_{16}H_{23}N_3O_2$	66.40	8.01	14.52	66.52	8.05	14.48	3220	3030	1665	1625
Et	*n*-Bu	B	127-128	97	$C_{16}H_{23}N_3O_2$	66.40	8.01	14.52	66.51	7.97	14.54	3230	3040	1665	1625
H	Et	B	186-187	40	$C_{12}H_{15}N_3O_2$	61.78	6.48	18.01	61.65	6.55	17.90	3240		1685	1645
C_5H_9	PhNH	B	176-177 (c)	14	$C_{21}H_{24}N_4O_2$	69.21	6.64	15.37	69.18	6.66	15.37	3200		1685	1645

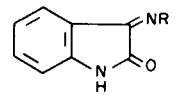
(a) Recrystallized from ethyl acetate unless otherwise noted. (b) Recrystallized from hexane. (c) Recrystallized from ethanol.



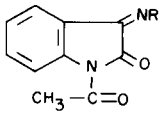
m/e 161 (40-100%) m/e 119 (22-25%)

With the exception of a shift of the NH protons to higher δ values, the nmr of IV is very similar to that of III.

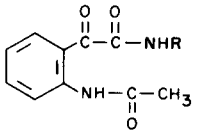
Although the hetero-ring of *N*-acetylisatin is opened by amines to provide a convenient route to compounds of the types III and IV, the reaction of *N*-acetylisatin with an equimolar quantity of phenylhydrazine proceeds in the normal manner to give the 3-phenylhydrazone of *N*-acetylisatin. The ring opening of *N*-acetylisatin by amines, which must involve nucleophilic attack at the 2-position, is contrasted with the behavior of isatin where, at least with equimolar quantities of amines, attack takes place at the 3-position and can be accounted for by the potential enolic structure of *N*-acetylisatin.



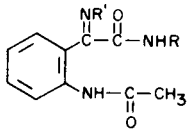
I



II



III



IV

EXPERIMENTAL

All melting points are corrected. Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Reaction of *N*-Acetylisatin and Amines (1:1).

A mixture of 0.01 mole of *N*-acetylisatin and 0.01 mole of an amine in sufficient 95% ethanol to dissolve them was heated on a steam bath for 30 minutes. After standing overnight the product (III) was obtained by filtration and recrystallization from the appropriate solvent to give the compounds in Table I. In a few cases a small amount of water was added to induce precipitation.

Reaction of *N*-Acetylisatin and Amines (1:10).

A mixture of 0.01 mole of *N*-acetylisatin and 0.1 mole of an amine were reacted as described above to give IV as indicated in Table II.

Reaction of III with Amines.

A mixture of 0.005 mole of III and 0.05 mole of an amine were reacted as described above to give IV as indicated in Table II.

Hydrolysis of IV (R = R′ = C_2H_5).

The compound (IV, R = R′ = C_2H_5) was dissolved in 5% hydrochloric acid and heated on a steam bath for 30 seconds after which time a white precipitate was obtained. Filtration and recrystallization from cyclohexane gave III (R = C_2H_5) which was identical with an authentic sample.

Acknowledgments.

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